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Valproic acid induced encephalopathy — 19 new cases in Germany from 1994 to 2003 — A side effect associated to VPA-therapy not only in young children

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Summary Valproic acid (VPA) is a broad-spectrum antiepileptic drug and is usually well-tolerated. Rare serious complications may occur in some patients, including haemorrhagic pancreatitis, bone marrow suppression, VPA-induced hepatotoxicity and VPA-induced encephalopathy. The typical signs of VPA-induced encephalopathy are impaired consciousness, sometimes marked EEG background slowing, increased seizure frequency, with or without hyperammonemia.

There is still no proof of causative effect of VPA in patients with encephalopathy, but only of an association with an assumed causal relation. We report 19 patients with VPA-associated encephalopathy in Germany from the years 1994 to 2003, none of whom had been published previously.

Sodium valproate (VPA) is a branched-chain fatty acid that is widely used in the therapy of epilepsy. The anticonvulsive action of VPA has been demonstrated to be due to a combined pharmacological effect of increased γ-amino-butyric acid (GABA) levels[1] inhibition of *N*-methyl-D-aspartat (NMDA)

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Table 1 VPA-induced encephalopathies with hyperammonemia

	Age (year)	Sex	Underlying disease	Retar-ded	EEG	VPA-level (mg/l)	ASAT U/l, ALAT U/l,	Ammonia (γmol/l) (11—55)	Add. AED	Add. disease	Outcome
1	65	M	Cerebri med. infarct	+	delta-focus	84.6	Normal	150	—	CHD, hypertonia	Recovery after withdrawal of VPA
2	4.6	F	Focal epilepsy	—	Generalized δ-activity	170	Normal	208	ETH	—	Recovery after withdrawal of VPA
3	1.9	F	Absence-epilepsy	—	Background slowing	[a]	38/33	111	—	Enteritis	Recovery after withdrawal of VPA
4	0.8	M	MELAS	+	Gen. δ-activity	[a]	4,—	258	PB, SUL, LTG,CL	Susp. of amino-acid metabolic disease	Recovery after withdrawal of VPA
5	2.6	M	Pseudo-Lennox-Gastaut	+	Background slowing	—	77, 36	159	TPM, ETH	Anaemia—	Recovery after withdrawal of VPA
6	16	F	IGE	—	Background slowing	74.5	Normal	261	—	—	Recovery after withdrawal of VPA

ALAT, alaninaminotransferase; ASAT, aspartat amino transferase; CHD, coronary heart disease; CL, clonazepam; ETH, ethosuximide; LTG, lamotrigine; MELAS, mitochondrial myopathy, encephalopathy, lactacidosis, stroke; OXC, oxcarbazepine; PB, phenobarbitone; SUL, sultiam; TPM, topiramate.

[a] Not done during encephalopathy.

Table 2 VPA-induced encephalopathies without or slight hyperammonemia

	Age (year)	Sex	Underlying disease	Retarded	EEG	VPA-level (mg/l)	ASAT U/l, ALAT U/l,	Ammonia (γmol/l) (11–55)	Add. AED	Outcome
1	52	M	Focal epilepsy	–	Theta-focus	63.6	–	Normal	CBZ, PB	Recovery after withdrawal of VPA
2	76	F	Cerebri med. infarct	+	Theta-focus	84.6	–	–	–	Recovery after withdrawal of VPA
3	77	F	Post-haemorrhage epilepsy	+	Background slowing	140	–	–	–	Recovery after VPA-reduction
4	28	M	Schizenzephaly	+	–	–	–	Normal	TPM, LEV, CL	Recovery after withdrawal of VPA
5	32	F	Epilepsy	–	Background slowing	75	–	Normal	CMZ	Recovery after withdrawal of VPA
6	41	M	Epilepsy	+	Background slowing, poly-spike-waves	–	Normal	Normal	PB, PHT	Recovery after withdrawal of VPA
7	63	F	Post-haemorrhage epilepsy	+	Background slowing	–	124, 28	–	PB, PHT	Recovery after withdrawal of VPA
8	64	M	Hypoxic brain damage	+	Background slowing	95.7	Normal	23	–	Recovery after withdrawal of VPA
9	74	F	Primary generalized epilepsy	–	Background slowing	95.2	23, –	–	–	Recovery after withdrawal of VPA
10	4.5	F	IGE	–	Background slowing	78	Normal	Normal	PB	Recovery after withdrawal of VPA
11	2.6	F	Bourneville Pringle	+	Background slowing	143.6	52, 436	68	OXC, LTG, CL	Recovery after withdrawal of VPA
12	72	F	Cerebri post. infarct	–	Delta-focus	–	Normal	64	–	Recovery after withdrawal of VPA
13	19	M	Focal epilepsy	–	Generalized δ-activity	72.1	Normal	69	–	Recovery after withdrawal of VPA

CBZ, carbamazepine; CHD, coronary heart disease; CL, clonazepam; IGE, idiopathic generalized epilepsy; PB, phenobarbitone; TPM, topiramate.

receptors[2] and a blockade of neuronal sodium channels.[3] VPA also effects a variety of different metabolic pathways and the compositing of membranes.[4]

Most of the side effects are mild and transient. However, more serious adverse reactions can occur such as hepatotoxicity,[5] encephalopathy,[6] coagulation disorders[7] pancreatitis[8] and bone marrow suppression.[9]

Three forms of encephalopathy in children and adults treated with VPA have been described: encephalopathy as direct toxic effect of VPA, with high serum levels of VPA but normal ammonia,[10] hyperammonemic encephalopathy[11] and encephalopathy with impaired liver function.[12] Encephalopathy was reported as an extremely rare complication of VPA therapy, described mostly in patients with inborn errors of metabolism, but also in patients without a known metabolic defect.[13]

Several publications showed an increased risk of encephalopathy when VPA was combined with topiramate.[13,14]

Direct drug effect on neurotransmitters is generally considered to be the main mechanism of VPA-induced encephalopathy.[15] VPA may lower glutamine synthesis via inhibition of glutamine synthase, thus contributing to hyperammonemia.[16] Another possible mechanism is direct neuronal toxicity induced by increased intracellular concentrations of glutamate and ammonium in astrocytes[17] which may lead to potential neuronal injury and perhaps cerebral edema.[18] It is not clear, whether changes in citrullinogenesis or in other steps of the urea cycle account for the increase of blood ammonia induced by valproate.[19] Up to 20% of asymptomatic patients treated with VPA may have mild hyperammonemia.[20]

We report 19 patients with VPA-induced encephalopathy in Germany from the years 1994 to 2003, none of whom had been published previously.

Since 1979, 51 cases of VPA-associated encephalopathy were reported in the literature.[5,6,21–34] Additionally, 13 cases of VPA-associated encephalopathy were reported in combination with TPM.[7,13,14,35–37]

Methods

We sent a questionnaire asking for side effects of VPA therapy from 1994 to 2003, to all 1200 members (Paediatricians, Neurologists) of the ''German Section of the International League against Epilepsy''. We specially inquired about severe side effects such as hepatopathy, pancreatitis, encephalopathy and coagulation disorders. The physicians were also asked for the anonymisized patient files in order to obtain details like VPA-dosage, laboratory parameters, the history and the outcome of the patients.

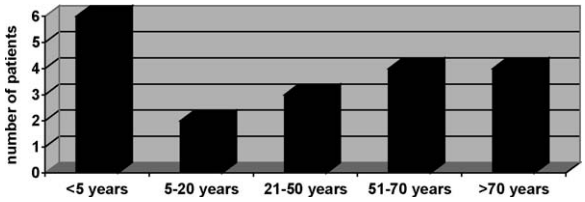

Figure 1 Age distribution of VPA-induced encephalopathies.

Results

In the last 10 years altogether 19 cases of VPA-induced encephalopathy were reported in Germany by members of German Section of the International League against Epilepsy. We analyzed the medical files of these 19 patients. Another eight patients were reported but we were not able to study the complete files. These patients were therefore omitted.

Tables 1 and 2 present details of the 19 patients, divided into two subgroups: patients with encephalopathy and hyperammonemia and patients with normal serum-ammonia or slight hyperammonemia (69, 68 and 64 γmol/l).

The average age of the patients was 38.6 years; the age distribution is shown in Fig. 1.

Eight of the patients were male, 11 female. Ten patients were mentally retarded, most of them children with infantile brain damage, only one had an inborn metabolic disorder (MELAS-syndrome). The VPA-treatment was started before the metabolic disorder was known.

All patients recovered after withdrawal of VPA. A 76-years-old women showed a prolonged onset with a slow recovery over 4 months. This patient was transferred to a nursery home when the encephalopathy began, but was able to live on her own again after the withdrawal of VPA. She additionally suffered from a Parkinson-syndrome, which may explain the prolonged normalisation.

VPA-induced encephalopathy may also occur at normal or slightly increased ammonia levels,[38] which was the case in 13 of our patients. Six patients, on the other hand, showed increased ammonia level. The average level was 191.2 γmol/l (111–259 γmol/l) (Table 1).

Discussion

VPA-induced encephalopathy is an important and severe side effect of AED-therapy. In contrast to

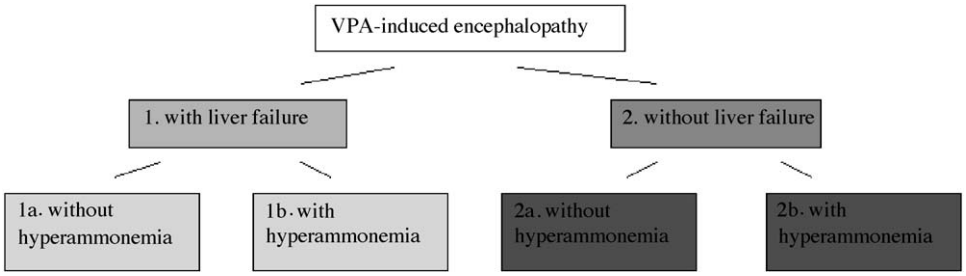

Figure 2 Possible types of VPA-induced encephalopathy.

previous publications, not only young children with metabolic defects were affected in our series, but also adults.

Nevertheless, neurological disabilities and metabolic disorders were a risk factor for VPA-induced encephalopathy.

The following four types of VPA-induced encephalopathy have to be distinguished.

- (1a) Encephalopathy with normal ammonia in 13 patients in our study, a direct effect on neurotransmitters postulated.[15]
- (1b) Encephalopathy with hyperammonemia without liver failure in six patients in this study—an inhibition of urea cycle is considered to be the pathomechanism, but this could not be the only reason, because some patients show encephalopathy with a moderate hyperammonemia by inhibiting the urea cycle, some do not.
- (2a) Encephalopathy with hyperammonemia and liver failure. Within our questionnaire we have found nine cases of lethal hepatopathies, with increased ammonia levels (average 271 γmol/l) and signs of an encephalopathy (fatigue, nausea and EEG-slowing). Additionally, apathy, EEG-slowing and hyperammonemia was found in 5 of the 16 patients (31%) in the series of Scheffner and Koenig.[39]
- (2b) Encephalopathy without hyperammonemia but liver failure: 31 cases of reversible hepatotoxicity (with and without hyperammonemia). 4/31 cases showed normal ranges of ammonia but the above described signs of encephalopathy (not regarded here but in a separate paper) (Fig. 2).

For sure it is by all means possible to have the same pathophysiological mechanism leading to the encephalopathy 2a and 2b.

On the other hand, there are patients (up to 20—50% in the series of Laub, Altunbasak and Verrotti[20,40,41]) that have a slightly elevated serum ammonia without clinical abnormalities. This can be considered an effect of the inhibition of the urea cycle by VPA. Although, there is still a lack of evidence to this hypothesis. We do not routinely measure ammonia in asymptomatic patients, as clinical consequences in these patients cannot be derived but patients and physicians are irritated without any reason.

From 1979 until now 51 patients with VPA-induced encephalopathy have been published in the literature. We found, however, 19 patients only in Germany in the last 10 years, in opposition to the statement, that VPA-associated encephalopathy is an extremely rare side effect. We therefore believe that the occurrence of this severe side effect is underestimated as reversible side effects are less likely to be published.

VPA-induced encephalopathy should also be considered in patients with rapidly progressing severe dementia who are treated with valproate. These patients should receive an EEG and blood tests for serum ammonia, liver enzymes and VPA-serum-level.

Fortunately all patients with VPA-induced encephalopathy but normal transaminases and normal coagulation can be expected to recover after withdrawal or reduction of VPA.

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